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10/803,180	03/18/2004	Michele Cargill	CL001511	6182

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,180	CARGILL ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 27-65* is/are pending in the application.

4a) Of the above claim(s) *46-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,27-45 and 56-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 27-65 are pending.
Claims 2-26 are cancelled.
Claims 46-55 are withdrawn.
Claims 1, 27-45, and 56-65 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 05/21/2007. Claim(s) 2-26 is/are cancelled; claim(s) 46-55 is/are withdrawn by the Examiner; claim(s) 27-65 has/have been newly added; claim(s) 1 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Election / Withdrawn Claims

1. Applicants elected with traverse of the invention of Group I (methods for identifying an individual who has an altered risk for developing an autoimmune disease using nucleic acid based methods to detect SNPs), as well as the particular disease rheumatoid arthritis (RA) and the polymorphism of hCV163035 (which is also disclosed in the specification as rs2276864 and SEQ ID NO: 5502), in the reply filed on 09/26/2006. The requirement was deemed proper and made final in the Office Action of 12/19/2006.

2. Newly submitted claims 46-55 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

> Newly presented claims 46-55 are specifically drawn to methods related to risk of myocardial infarction, where the particular disease is distinct from the Elected RA (as discussed in the Requirement for Restriction of 7/26/06 and the Office Action of 12/19/2006).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 46-55 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

3. The IDS submitted on 5/21/2007 has been considered.

Specification

4. Applicants remarks concerning the objection to the specification as different SEQ ID NOs which identify identical sequences has been considered and is found to be persuasive. The objection to the specification is **WITHDRAWN**.

Withdrawn Claim Objections

5. The objection to claims for specifically reciting non-elected subject matter is **WITHDRAWN** in light of the amendments to the claims.

New Claim Objections

6. Claim 29, 39, 49, and 59 are objected to over recitation of the phrase 'the genomic of TRIP gene' as recited in each of claims 29, 39, 49, and 59, where likely the phrase 'the genomic of the TRIP gene' is intended. Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

7. The rejection of claims under 35 USC 112 2nd¶ as indefinite, as presented in the previous Office Action, are **WITHDRAWN** in light of the amendments to the claims.

New Grounds of Rejection

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 29, 32, 39, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 39, and 59 are unclear over recitation of the phrase 'as represented by', as recited in each of claims 29, 39, and 59, in reference to the relationship between 'SEQ ID NO: 1688' and 'the genomic sequence of TRIP gene'. The specification does not define what elements (e.g. percent identity of percent similarity) are required for any gene to be 'represented by' any particular SEQ ID NO. Thus it is unclear if Applicants are in fact requiring some particular sequence context for the detected polymorphism at position 101 in SEQ ID NO: 5502.

Claim 32 is unclear over recitation of the phrase 'said biological sample' because there is no proper antecedent basis for any 'biological sample' in either claim 32, or claims 1 or 28 from which claim 32 depends. See MPEP 2173.05(e).

Maintained Claim Rejections - 35 USC § 112 1st - Written Description

10. Claims 1 and 27-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> Applicant is referred to the guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov); also MPEP 2163.

The rejected claims are drawn to methods comprising detecting a single nucleotide polymorphism (SNP) at position 101 o SEQ ID NO: 5502 or its complement, wherein the presence of the SNP is correlated with an altered risk for RA. The claims are thus broadly drawn to methods comprising the detection of a variety of nucleic acids, including any SNP variant at position 101 of SEQ ID NO: 5502 that is associated with an altered risk for RA.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the detection of a variety nucleic acid sequences. The claims are drawn to a plurality of nucleic acids that encompass a genus of SNP variants in which position 101 SEQ ID NO: 5502 may have any nucleotide content (A or G or C or T, as well as a deletion or insertion of any nucleotide (specification page 6 lines 12-19). Thus the claims encompass at least the detection of any of 9 different nucleic acids (i.e. any of four substitutions at position 101, or any of four insertions at

position 101, or a deletion of position 101) wherein the nucleic acid sequence is correlated with any altered risk for RA. Nucleic acid members of this genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID NO: 5502 as well as the identical sequence in SEQ ID NO: 1658 wherein the nucleotide at position 101 is indicated to be polymorphic and can be either an A or a G, and provides an analysis indicating that the presence of an A is correlated with an decreased risk of developing RF+ RA. The specification does not provide any other polymorphic positions of SEQ ID NO: 5502 that would result in any other alteration in the sequence disclosed as SEQ ID NO: 5502 that is correlated with any altered risk for any RA. With specific regard to claims 56-65, while the claims specify a nucleotide content at position 101 of SEQ ID NO: 5502 (i.e. either a C or a T), it is noted that the claims do not provide any language regarding the complement of the required SEQ ID NO, and the specification does not provide for identification of a C or T at position 101 of SEQ ID NO: 5502 as required by the claims (the specification indicates that position 101 of SEQ ID NO: 5502 may be either an A or a G).

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not

provide any characteristics that would allow the identification of the broadly claimed SNPs in SEQ ID NO: 5502 other than the A/G at position 101 (or a T/C at position 101 of the complement of SEQ ID NO: 5502) which would allow for the identification of an individual who has an altered risk for developing RA. Neither the instant specification nor the prior art provide guidance as to how one would a priori identify any of the broadly claimed SNP at position 101 of SEQ ID NO: 5502 that is indicative of a particular alteration in the risk of developing RA.

Applicants' attention is directed to the decision in In re Shokal, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, the specific information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for identification of an individual with an altered risk for developing RA by determining the presence of a SNP in SEQ ID NO: 5502 other than methods using the A/G SNP at position 101 of SEQ ID NO: 5502.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ for lack of adequate written description. Applicants argue (p.8 of Remarks) that the claims specify a single polymorphisms SNP hCV163035, rs2276864, within SEQ ID NO: 5502, which is associated with an altered risk of RA. This argument in light of the amendments to the claims has been considered but is not found to be persuasive. As detailed in the rejection, the specification provides specifically for either A/G content at position 101 of SEQ ID NO: 5502 (or C/T content at position 101 of the complement of SEQ ID NO: 5502) as associated with altered risk of RA. The claims still encompass methods comprising the detection of sequences not described in the specification as being indicative of altered risk of RA; the claims encompass the detection of any nucleotide content at position 101 of SEQ ID NO: 5502 (e.g. claims 1 and 28-45), and with regard to claims 56-65 the claims specifically require detection of C or T at position 101 of SEQ ID NO: 5502, where the claims do not recite or require that the particular nucleotide content is detected in the complement of SEQ ID NO: 5502.

It is noted that claims 56-65 are not rejected for lack of adequate written description because the claims specify the detection of particular nucleotide content at position 101 of SEQ ID NO: 5502. However, the claims are rejected for lack of enablement as discussed below in this Office Action.

The rejection as set forth is **MAINTAINED**.

Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 28-45, and 56-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for,

> A method for identifying a human individual who has a decreased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids;
> detecting the nucleotide content at position 101 of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide A at position 101 of SEQ ID NO: 5502 identifies the individual as having a decreased risk for developing RF+ RA.

does not reasonably provide enablement for methods comprising the detection of the presence of a G at position 101 of SEQ ID NO: 5502 (other than detection of G G homozygosity of position 101 of SEQ ID NO: 5502 being indicative of an increased risk of RA), or identification methods comprising correlating any other nucleotide content at any other position in SEQ ID NO: 5502 with any form or RA other than RF+ RA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for identifying an individual who has an altered risk for developing RA.

The claims encompass detecting any SNP broadly claimed as 'a SNP at position 101 of SEQ ID NO: 5502'.

The claims broadly encompass methods in which detection of a SNP is correlated with any altered risk (i.e. increased risk or decreased risk) of any form of RA.

The nature of the inventions requires knowledge of an association between broadly claimed nucleic acid content and altered risk of having RA.

Direction provided by the specification and working example

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.28 – p.8 ln.4).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 5502, which may be either an A or a G, and is also identified as hCV163035 and known in the art as rs2276864. The specification teaches that the frequency of the particular allele was analyzed in two (p.120 ln.26 – p.121 ln.11) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that the Replication set was

analyzed in totality (i.e. an 'all' stratum) after stratification of the subjects into an RF+ stratum (p.12; p.121 ln.28).

The specification teaches the specific association of the A allele (i.e. an A nucleotide a position 101 of SEQ ID NO: 5502) with a decreased risk of RA as the A allele is found at a significantly higher frequency in control samples in the Discovery Set and the Replication Set (Table 6;). It is noted that Table 6 designates the 'T' allele as associated with the decreased risk of RA, and the specification indicates that nucleotide content may be described as the reverse of the nucleotide content at the position (e.g. p.20, lns.25-30), thus the T allele of the reverse complement of SEQ ID NO: 5502 is the A allele of SEQ ID NO: 5502. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+ (p.120 ln.29). While the instant specification provides that the A allele is indicative of a decreased risk for RA in the Replication Set in the 'All' Stratum, the specification provides no indication as to how many of the cases in the Replication Set were either RF+ or RF- (i.e. while the specification indicates that the Replication Set had 840 patients, it is not known if there were enough of both RF+ and RF- individuals to make data regarding the 'All' stratum significant for both RF+ and RF-). Thus it is not possible to determine from the data of Table 6 indicating a significant relationship between the A allele of SEQ ID NO: 5502 and decreased risk of RA is in fact significant within the RF- population of cases under analysis. Thus while the data of specification teaches an association of the A allele with decreased risk of RF+ RA, it is not clear from the

specification if the A allele is specifically associated in the same way, or in a significant fashion, with RF- RA.

Because the claims encompass detection of only one of either allele (it is noted that claim 56 encompasses making a determination based on the detection of either a C or a T at the polymorphic position), where determination of heterozygosity at the position (i.e. and individual with one of each allele) would be detection of both alleles, it is relevant to point out that the data presented in the instant specification (i.e. Table 6) indicates only that the presence of a T allele (which is an A allele in SEQ ID NO: 5502) is indicative of a decreased risk of RF+ RA. The data does not stratify the data based on genotype (i.e. CC vs CT vs TT), and thus appears to present only that detection of a T allele (i.e. either in a CT or TT genotype) is indicative of decreased risk of RF+ RA as compared to a CC individual, and does not provide a comparison of the relative risk of RF+ RA in a CT versus a CC individual. Thus while it is possible for the data to support that the presence of an A at position 101 of SEQ ID NO: 5502 is indicative of decreased risk of RF+ RA (because presence of either an AA or AG genotype would have a decreased risk), the data would not support making a determination based only on the presence of a single G allele (because it would not be known if the individual has a GG (increased risk) genotype or an AG (decreased risk) genotype).

The instant specification provides only the association analysis of either an A or a G at position 101 of SEQ ID NO: 5502 (as consonant with the Election), and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 5502.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach an association between any polymorphism at position 101 in SEQ ID NO: 5502 and altered risk for developing RA. And because the claims encompass the detection of a variety of polymorphic nucleotide content at position 101 of SEQ ID NO: 5502, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Because the claims encompass identifying an altered risk of any form of RA (e.g. RA that is either RF+ or RF-), it is relevant to point out that the instant specification does not particularly indicate an association between the nucleotide content of position 101 of SEQ ID NO: 5502 and RF- RA. It is relevant to point out that the post filing art indicates a difference in the genetics underlying the RF+ versus the RF- forms of RA. For example, the post filing art of Harrison et al (2006) indicates that an allele of the SNP identified as rs2476601 is associated with RF+ RA but not associated with RF- RA

(p.1010, left col., 1st ¶ of Results; Table 1; p.1011, left col., Key messages box). Similarly, Lee et al (2005) teach that the same rs2476601 polymorphism is not associated with RF- RA (p.129 – Abstract; p.130, right col., lns.5-15; Table 1), and Begovich et al (2004) indicate that an allele of rs2476601 (p.331, left col., lns.14-15) is not significantly associated with the RF- form of RA (Table 3; p.333, right col., lns.9-13). In an analysis of the association of an FcγRIIIa polymorphism with RF+ and RF- RA, Chen et al (2006) reports a significant skewing of the observed distribution of the 'F' allele with the RF- form of the disease (p.10 – Summary; Table 1; p.12, right col., lns.4-7). Given the lack of any RF- versus RF+ stratification of the population examined by the examples of the instant specification, and the teachings in the art with regard to the genetic differences of the RF+ versus the RF- forms of RA, it is unpredictable as to whether or not the nucleotide content of position 101 of SEQ ID NO: 5502 is reliably associated with increased risk of the RF- form of RA.

Quantity of experimentation required

A large amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would include examining an association of any nucleotide content at position 101 of SEQ ID NO: 5502 with the risk of RA. This would involve large case:control studies in multiple human populations, and the analysis of different polymorphic variants of SEQ ID NO: 5502. Even if such an analysis were to be performed, there is no guarantee that one would find any significant associations beyond those specifically taught in the particular example of the instant specification.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement. Applicants have argued (p.8-10 of Remarks) that the data presented in the instant application is enabling for detection of increased risk of both RF- RA and RF+ RA.

Applicants have traversed the Examiner's rejection, where the rejection is based on a lack of stratification of the presented data such that the data does not show a specific correlation between the presence of nucleotide content at position 101 of SEQ ID NO: 5502 and RF- RA, by presenting the van Oene (2005) reference. Applicants assert that van Oene et al demonstrates that a particular allele of PTPN22 is associated with both RF- RA and RF+ RA. The argument and reference have been considered but are not found to be persuasive. Initially it is noted that van Oene et al do not perform a particualr analysis of both RF- RA and RF+ RA, but rather perform an analysis of a combined population that includes both RF- RA and RF+ RA patients. As such the conclusion of van Oene et al that association of the risk allele with RA is not affected by presence of rheumatoid factor (p.1993, right col., Results) is different than performing

separate analyses of both patient populations to concluded that a risk allele is in fact associated with both RF-RA as well as RF+ RA. In this situation, the data of Lee et al and Harrison et al (as cited in the rejection) in which the RF- and RF+ populations were examined as separate groups, is more convincing in demonstrating that in fact the risk allele is not associated with the RF- form of RA.

Applicants have further argued that a lack of association of the PTPN22 risk allele with RF- RA demonstrated by Begovich et al (as cited in the rejection) may be explained by the small sample size of RF- RA patients. In this case it is noted that that sample populations examined by Begovich et al appear to be very similar to the sample population examined in the data presented in the instant application, and lack of an adequate sample size is not considered evidence that a particular association exists.

Finally, it is noted that van Oene et al perform an analysis of an allelic variant (i.e. PTPN22 R620W, also known as rs2476601) (also analyzed in Harrison et al, Chen et al, and Begovich et al) distinct from the particular SEQ ID NO: 5502 of the instant claims. Thus while it may be true, as argued Applicants, that it is evident to one with ordinary skill in the art that the same SNP could be associated with risk of RA in both RF+ and RF- patients, none of the references cited in the Office Action serve to provide evidence that the relevant SNP (i.e. hCV163035, also know as rs2276864, identified in the instant application as SEQ ID NO: 5502) is in fact associated with both RF+ RA as well as RF- RA.

It is noted that with regard to the rejection of newly presented claims 56-65, the claims specifically require that, for example, the presence of T at position 101 of SEQ ID

NO: 5502 in indicative of decrease risk of developing RA, where the specification indicates that position 101 of SEQ ID NO: 5502 may be either an A or a G. The claims are not drawn to the complement of SEQ ID NO: 5502, wherein the polymorphic position may be a C or a T. Furthermore, as detailed in the rejection, the data presented in the specification (Table 6) supports only the identification of an A at position 101 of SEQ ID NO: 5502 (i.e. identification of either an AA or AG genotype) as indicative of a decreased risk of RF+ RA); the data does not support the detection of a single G (or C in the complement) allele as indicative of an increased risk of RF+ RA.

The rejection as set forth is **MAINTIANED**.

Claim Rejections - 35 USC § 102

13. The rejection of claims under 35 USC 102 as anticipated by the prior art is **WITHDRAWN** in light of the cancellation of the rejected claims.

Conclusion

14. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER